disease.[6] Palmu and colleagues' study complements their previous findings with this investigation of the effect of PHiD-CV10 on secondary endpoints—non-culture-confirmed, but suspected episodes of invasive pneumococcal disease.

The figure provides a schematic representation of the findings from the study by Palmu and colleagues and contrasts these with the previously reported efficacy estimates of PHiD-CV10 in the prevention of culture-confirmed invasive pneumococcal disease. For a fixed 100 000 person-years of follow-up, the number of episodes of invasive pneumococcal disease expected in the absence of vaccination for each endpoint (irrespective of serotype) was estimated from incidence rates in children not randomly assigned to PHiD-CV10. Vaccination with PHiD-CV10 prevented invasive pneumococcal disease episodes. The figure also shows residual disease was present after vaccination, probably due to disease caused by non-vaccine serotypes, vaccine failure, or as a consequence of poor endpoint specificity. PHiD-CV10 vaccination resulted in high relative efficacy when the primary endpoint of culture-confirmed invasive pneumococcal disease was used, and roughly 61 such episodes were prevented.[5] When the more sensitive but less specific non-culture-confirmed endpoints were assessed with verified suspected and all suspected invasive pneumococcal disease, the relative efficacy estimates decreased but the estimated number of prevented episodes was 2·3 and 3·4 times larger than were the reductions in culture-confirmed episodes, respectively. Thus, a large number of invasive disease episodes prevented were missed when investigators relied solely on culture-confirmed detection.

The finding of increased absolute reductions in the burden of disease by use of sensitive rather than specific endpoint definitions is important for decision making about vaccination policies, and should serve as a lesson, both for trials and for continuing surveillance of vaccine effectiveness. As Palmu and colleagues show, results based on cultures for detection of invasive pneumococcal disease can suggest a misleadingly low burden of disease, and the number of prevented cases estimated with this strategy might seem insufficient to trigger action.[1,7] With the powerful framework of a randomised study design, the investigators show that the benefits of vaccination with pneumococcal conjugate vaccines extend far beyond traditional culture-confirmed detections.

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Dose and timing of prenatal tobacco exposure: threats to early child development

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For more than 50 years, we have known that prenatal tobacco exposure increases a child's risk of low birthweight and prematurity.[1] Recent studies have shown that in addition to negative growth and health consequences,[2] prenatal nicotine exposure increases the risk of a wide range of behavioural and developmental problems, including attention deficit hyperactivity disorder,[3] conduct disorders,[4] externalising behaviour problems,[5] and adolescent tobacco use.[6] Although associations with cognition and language problems have been reported, they are less strong and enduring than the associations with behaviour problems.[7]

Maternal tobacco use exposes the fetus to more than 7000 chemicals, including nicotine. Nicotine acts as a


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stimulant within the reward pathways and the nicotine receptors throughout the body, and is thought to cause hypoxia, to disrupt the nutrient supply, and to cause vasoconstriction of the placenta and umbilical vessels. The mechanisms linking nicotine to brain development are less clear, but might work through changes in metabolism and the neurotransmitter systems.[8] These effects could vary by dose and timing of the nicotine exposure; exposure during the embryonic stage is likely to cause different effects from exposure later in pregnancy. The other chemicals in tobacco smoke might also play a part in disrupting early brain development; few have been studied individually.

Sue Cooper and colleagues[9] report the effect of nicotine replacement therapy patches in 1050 pregnant smokers recruited at 12–24 weeks' gestation. Their finding that the intervention group experienced a reduction in smoking (validated by carbon monoxide concentration, salivary cotinine concentration, or both) 1 month after enrollment suggests that children in the intervention group had a varying period of lower tobacco exposure in the second-third trimester, despite no differences in smoking at delivery. The subsequent finding of higher rates of survival with no developmental impairment at 2 years of age in the intervention group suggests that the nicotine patch was not harmful and could have reduced children's prenatal tobacco exposure. However, questions arise regarding the mechanisms, including the timing and reduction in dose of tobacco are necessary to achieve a positive effect. No differences in birthweight, gestational age, or other birth outcomes were noted, suggesting that the mechanisms affecting the tobacco–growth association differ from the mechanisms guiding the tobacco–brain development association. No information is provided about the children's nutritional status at 2 years or about other environmental conditions that might affect early development. The absence of differences in rates of maternal smoking at the child's age of 2 years and the low rates of smoking cessation (<3%) indicate that more effective methods of smoking cessation during pregnancy are necessary. The finding that nicotine causes cell damage and impairs synaptic activity has led to the recommendation of caution in the dose and timing of nicotine patches during pregnancy, especially if women continue to smoke.[10]

A strength of the Cooper and colleagues'[9] is the prospective assessment and the focus on child development at 2 years. Although early child development is the genesis of adult health and wellbeing, many studies of smoking cessation during pregnancy terminate at delivery with the birthweight and gestational status of the newborn. By examination of children's development beyond infancy, this Article generates a hypothesis by showing the need to address variability in the dose and timing of prenatal exposure to nicotine and other tobacco toxins.

A 2014 report from the US Surgeon General[11] emphasises that prenatal nicotine exposure during fetal development adversely affects maternal and fetal health during pregnancy, with lasting adverse consequences for brain development. In view of the negative consequences of prenatal nicotine and other tobacco toxin exposure worldwide, WHO recommends that pregnant women abstain from smoking.[12] The effectiveness of tobacco-control programmes varies widely across countries. Data from 15 European countries suggest that 26·2% of women smoke during pregnancy.[13] In the USA, data from the National Survey on Drug Use and Health,[14] indicate that in 2009–10, tobacco use in non-pregnant women was estimated at 26·7%, compared with 16·3% in pregnant women. In adolescents aged 15–17 years, the rate of smoking was higher in pregnant women (22·7%) than in non-pregnant women (13·5%). Increases in electronic-cigarette advertising and use in the youth throughout the world are further causes for concern.[15]

Three primary research agendas are urgently needed. The first is an understanding of the mechanisms whereby smoking during pregnancy disrupts prenatal brain development and functioning; convincing evidence shows that brain disruption occurs.[4,8,11] Advanced neurophysiological and neurodevelopmental methods can provide additional evidence regarding the dose and timing of the nicotine exposure, along with exposure to the other chemicals, on fetal brain development. A second agenda involves investigation of the effect of electronic cigarettes and other nicotine-containing vapour devices, and nicotine replacement patches used during pregnancy. The third agenda is the development and evaluation of effective tobacco prevention and control strategies. Smoking rates in women are increasing globally, particularly in countries with low and middle incomes where there is often intensive marketing and little attention to the negative consequences of

smoking during pregnancy.[16] Incorporating issues of empowerment and the social context of women into gender-based strategies for tobacco control could be an effective strategy to reduce smoking during pregnancy[13] and to promote the health, development, and wellbeing of women and children.

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Bronchiectasis trials: losing the battle but winning the war?

The past several years have seen a growing interest in bronchiectasis from clinicians, academia, and industry. Having previously relied on extrapolating evidence from cystic fibrosis, this renewed interest is now translating into a number of large randomised trials, specifically in bronchiectasis. These efforts include recently published phase 3 trials of dry powder mannitol,[1] colistin,[2] and now in the *Lancet Respiratory Medicine*, inhaled aztreonam for patients with chronic Gram-negative airway infection.[3]

This landmark study is the largest randomised trial in bronchiectasis so far conducted. 266 patients in AIR-BX1 and 274 patients in AIR-BX2 were included in two identical double-blind placebo-controlled trials to assess the efficacy and safety of two 28-day courses of inhaled aztreonam. The authors chose health-related quality of life as the primary outcome, using the newly developed Quality of Life-Bronchiectasis (QOL-B) questionnaire. The study seemed set to provide both a new treatment for bronchiectasis and a new validated clinical trial endpoint.

Sadly, the trial's primary endpoint was not met, and 22% of aztreonam-treated patients (29 of 134) discontinued treatment because of intolerance in AIR-BX1 (*vs* 3% [four of 132] in the placebo group), and 8% (11 of 135) discontinued aztreonam in AIR-BX2 (*vs* 3% [four of 137] in the placebo group.[3] Adverse effects were mostly respiratory (dyspnoea and cough), mirroring effects noted with previous inhaled agents such as tobramycin.[4] Despite extensive subgroup analyses, a clear responder population could not be identified.

Why did this therapy, which is effective in cystic fibrosis,[5] not benefit patients with bronchiectasis? Some aspects of the study design might have contributed. The study included a broad, heterogeneous population of patients, including a mix of aetiologies, different Gram-negative pathogens, and a range of severities. What

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